REMARKS/ARGUMENTS

With entry of this amendment, claims 3-7, 9, 11, 16, 18-20, 24-26, 32, 34-38 and 39-44 are pending. Claims 3-6, 16, 18, 24-26 and 34-36 are allowed. Claims 7, 9, 11, 32, 37 and 38 are rejected. Claims 19, 20 and 26 are objected to. Claims 7, 9, 11, 19, 20, 26, 32, 37 and 38 are amended. Support for amended claim 7 can be found, for example, at page 12, lines 23-35 and page 14, lines 16-22. Support for amended claims 9, 11 and 32 can be found, for example, at page 13, lines 14-17. Support for amended claims 19 and 20 can be found, for example, at page 21, lines 12-15. Support for amended claim 26 can be found, for example, at page 1, lines 29-31. Support for amended claim 37 can be found, for example, at the following: page 10, lines 24-26; page 11, line 35 to page 12, line 6; page 13, lines 14-25; page 23, lines 22-26; and Figure 4B. Support for amended claim 38 can be found, for example, at the following: page 13, lines 14-17; page 16, lines 28-34; page 34, lines 32-34; page 35, lines 17-27, and p. 16, line 13 to p. 17, line 10.

New claims 39-44 are added. Support for new claim 39 can be found, for example, at the following: page 18, line 15 to page 19, line 17; page 13, lines 14-25; page 23, lines 22-26; and Figure 4B. Support for new claim 40 can be found, for example, at the following: page 18, line 15 to page 19, line 17; page 13, lines 14-17; page 16, lines 28-34; page 34, lines 32-34; and page 35, lines 17-27. Support for new claim 41 can be found, for example, at page 13, lines 14-25. Support for new claim 42 can be found, for example, at page 13, lines 14-22 and at page 16, lines 28-34. Support for new claim 43 can be found, for example, at the following: page 18, line 15 to page 19, line 17; page 13, lines 14-25; page 23, lines 22-26; and Figure 4B. Support for new claim 44 can be found, for example, at the following: page 18, line 15 to page 19, line 17; page 13, lines 14-25; page 23, lines 22-26; and Figure 4B. No new matter is believed to be added by these amendments.

No claim amendment should be construed as acquiescence in any ground of rejection.

Claim Objections

Claims 19, 20 and 26 stand objected to as allegedly redundant or having a non-defined abbreviation. Claims 19, 20 and 26 have been amended in accordance with the Examiner's suggestion. Claims 19 and 20 are amended to recite a "pharmaceutical preparation." Claim 26 is amended to set forth the full name of ß-APP, ß-amyloid precursor protein.

35 U.S.C. § 112, second paragraph, indefiniteness

Claims 9, 32 and 37 stand rejected as allegedly indefinite. Claims 9, 32 and 37 have been amended in the manner suggested by the Examiner. Claim 9 is amended to recite the peptide fragment comprises, as the C-terminal 14 amino acids, SEQ ID NO:9. Claim 32 is similarly amended to recite the protein comprises, as the C-terminal 14 amino acids, SEQ ID NO:9. Claim 37 is amended to recite, the peptide consists of a peptide motif of SEQ ID NO:9 wherein within the motif at least seven amino acids of SEQ ID NO:9 are conserved.

35 U.S.C. § 112, first paragraph, enablement

Claims 7, 11, 37 and 38 stand rejected as allegedly not enabled. The Examiner raises a number of points, each of which is addressed below.

The Examiner alleges claim 7 is overly broad and encompasses the production of any recombinant protein. Applicants understand the Examiner's underlying concern to be the recitation of "a recombinant protein." Claim 7 recites a method for producing a protein that is produced by culturing a host cell containing the DNA of claim 3. Claim 3 recites the DNA encodes a protein of claim 35. Thus, the recombinant protein produced in claim 7 is the protein recited in claim 35. Claim 35 has been allowed, confirming that claim is enabled. Therefore claim 7, which depends indirectly from claim 35, is enabled for the same reasons.

Without acquiescing to the rejection but to proceed with more compact prosecution of this case, Applicants amend claim 7 to clarify further that the recombinant protein produced by the host cell is encoded by the DNA of claim 3. Applicants respectfully submit the rejection of claim 7 is moot in view of this amendment.

The Examiner alleges claim 11 is overly broad and allegedly encompasses using fragments of any variant of SEQ ID NO:2-4 in a binding assay. However, "the protein" referred

to in step (a) of claim 11 has antecedent basis in the protein of claim 35 (see preamble of claim 11). Thus, insofar as claim 11 refers to "the protein," it is enabled for the same reason as claim 35. Insofar as claim 11 refers to fragments, the fragments are constrained by the requirement that the C-terminal 14 amino acids are SEQ ID NO:9. It is respectfully submitted that the specification does enable how to make and use such fragments.

Initially, Applicants note the Examiner does not contest that the specification teaches how to make peptide fragments of SEQ ID NO: 2-4. Applicants submit the specification also teaches how to make peptide fragments of variants of SEQ ID NO: 2-4 (*i.e.*, variants of SEQ ID NO: 2-4 having peptidase activity towards brain APP and in which not more than 30 amino acids are replaced, deleted, inserted and/or added). Such fragments can be produced, for example, by standard techniques of mutagenesis and recombinant expression.

The Examiner alleges the specification does not establish the activity of any fragment of any variant of SEQ ID NO: 2-4 in a binding assay. However, all fragments included in the claim comprise SEQ ID NO:9 and therefore have at least the activity of SEQ ID NO:9. The specification also discloses that antibody against SEQ ID NO:9 inhibits the proteolytic activity human brain CPB (p. 28, lines 34-36), implying that these C-terminal fourteen amino acids occur in the proteolytic domain and are involved in peptidase activity (*see also*, page 40, lines 2-17). Matsumoto *et al.* (*European J. of Neuroscience* 13:1653-57 (2001); submitted with this response) further confirms the role of this C-terminal sequence in the peptidase activity (*see* page 1657, left column). Therefore, polypeptides comprising SEQ ID NO:9 are useful for identifying inhibitors of brain CPB protease in screening assays. An initial binding assay (*see, e.g.*, p. 18, lines 15-22) narrows down the number of candidate molecules. A subsequent inhibition assay (and p. 19, lines 18-27) indicates which of the molecules surviving the binding assay actually have proteolytic activity. Thus, all of the polypeptides encompassed by claim 11 have the common feature of the recited peptide fragment, SEQ ID NO:9, and are useful in screening for protease inhibitors.

The Examiner next alleges the specification does not establish the region of any fragment of SEQ ID NO: 2-4 that can be modified without affecting the activity of the fragment in a binding assay, or the extent of such tolerance, and does not provide sufficient guidance as to

which of the essentially infinite possible choices of variant fragments are likely to be successful in identifying compounds that bind to SEQ ID NO: 2-4. Applicants respectfully disagree. As discussed above, the peptide fragments have at least one common binding activity, that of the C-terminal amino acids, SEQ ID NO: 9. This sequence is invariant in the recited peptide fragments. Other regions of the peptide fragments can be modified without affecting the binding activity of SEQ ID NO:9. All such peptides can be used in identifying antibodies and other compounds that bind to SEQ ID NO:9 and in screening for protease inhibitors.

For these reasons, Applicants respectfully submit claim 11 enabled.

The Examiner says claim 37 is overly broad and allegedly encompasses the production of any polypeptide comprising the motif of SEQ ID NO:9, wherein within said motif at least 7 amino acids are conserved. As discussed above, claim 37 has been amended to recite an isolated peptide consisting of a peptide motif of SEQ ID NO:9, wherein within said motif, at least 7 amino acids of SEQ ID NO:9 are conserved.

The Examiner alleges the specification does not establish the activity of any protein comprising a motif of SEQ ID NO:9, wherein within said motif at least 7 residues of SEQ ID NO:9 are conserved. Applicants respectfully disagree. As discussed above, SEQ ID NO:9 can be used in screening for compounds that inhibit proteolytic activity of brain CPB. The claimed genus of peptides, which include at least seven conserved amino acids of SEQ ID NO:9, are useful for the same purpose as SEQ ID NO:9. Some peptides having a core region of SEQ ID NO:9 responsible for proteolytic function may be more useful that SEQ ID NO:9 in screening for inhibitors. Other peptides may be less useful than SEQ ID NO:9 or have no advantage relative to SEQ ID NO:9 but can nevertheless still be used in a binding assay to reduce an initial pool of candidate compounds to a subset for which inhibitor activity can be determined in a confirmatory assay using a full-length brain CPB protease.

The Examiner says the specification does not establish the regions of the protein's structure that can be modified without affecting the activity of the protein, the general tolerance of the activity of said protein to modification, the extent of such tolerance or a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological activity. Applicants respectfully disagree. It is not necessary for the skilled artisan to

know in advance which amino acids can be modified. Any peptide encompassed by the claim can be used in a binding assay to identify compounds that bind to the peptide (as described in the specification at p. 18, lines 15-22). Although not all such compounds necessarily inhibit its activity, the binding assay to the peptide does reduce the number of candidate compounds for subsequent screening. A subsequent assay for protease activity (as described at *e.g.*, 19, lines 18-27) can determine which of the compounds identified by the binding assay have protease inhibitory activity.

The Examiner says claim 38 is allegedly overbroad so as to encompass any peptide variant of SEQ ID NO:9 in which no more than 5 residues have been altered, deleted, inserted and/or added. As discussed above, claim 38 has been amended to recite an isolated peptide variant of SEQ ID NO: 9 consisting of an epitope of human brain carboxypeptidase B, wherein no more than 5 amino acids of SEQ ID NO: 9 are replaced, deleted, inserted and/or added, and wherein the peptide variant binds to an antibody that binds to SEQ ID NO:2.

The Examiner alleges the specification does not establish the activity of any peptide variant of SEQ ID NO:9, in which no more than 5 residues have been altered, deleted, inserted and/or added. Applicants respectfully disagree. SEQ ID NO:9 is useful for obtaining antibodies (*see, e.g.*, specification page 13, lines 14-17), particularly antibodies that distinguish brain CPB from plasma CPB. Such antibodies are useful for detecting the claimed proteins (*see, e.g.*, p. 6, lines 21-25). The claimed genus of peptides are useful for the same purpose.

The Examiner further says the specification does not establish the regions of the peptide's structure that can be modified without affecting the activity of the protein. The Examiner also says the specification does not establish the general tolerance of the activity of said peptide to modification and the extent of such tolerance, and further says the specification does not establish a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological activity.

Applicants respectfully disagree. As amended, claim 38 requires that the claimed peptides binds to an antibody that binds to full length brain CPB (*i.e.*, SEQ ID NO:2). In other words, the claimed peptides are immunologically cross-reactive with the full-length protein. Such peptides can be recognized by a simple screen to determined that the peptide binds to

polyclonal sera to the full-length protein. Any peptide that does so bind can be used for the purpose of generating antibodies to the peptide. These antibodies are useful for detecting brain CPB as discussed above. For these reasons, Applicants respectfully submit that claim 38 is enabled.

Applicants therefore respectfully request the Examiner reconsider and withdraw the rejection of claims 7, 11, 37 and 38 under 35 U.S.C. 112, first paragraph.

35 U.S.C. § 112, first paragraph, written description

Claims 7, 11, 37 and 38 are rejected as allegedly lacking written description.

The Examiner rejects claim 7 for an alleged lack of functional written description and for insufficient structural written description. The Examiner says claim 7 is directed to a method of producing a genus of recombinant proteins, and alleges the genus of proteins to be a large variable genus with many different, functionally unrelated proteins. Applicants understand the Examiner's concern to be the same as that set forth in the preceding section for claim 7. As explained above, the recombinant protein recited in claim 7 is a protein of claim 35. Thus, it is respectfully submitted that Applicants have described sufficient representative species having the recited function within the recited genus. Applicants therefore submit the rejection is moot.

The Examiner says claim 11 lacks sufficient functional and structural written description. In particular, the Examiner says claim 11 is directed to a method of using a genus of peptide fragments of any variant of SEQ ID NO: 2-4 in a binding assay and alleges the specification does not contain any disclosure of the function of the peptide fragments of variants in a binding assay.

Structural description is provided by the recitation that fragments have no more than 30 amino acids replaced, deleted, inserted and/or added relative to SEQ ID NOS:2-4, and further have a common structural feature, SEQ ID NO:9 as the C-terminal amino acids. These structural features allow one to visualize any species encompassed within the claim. The structural features commonly possessed by members of the claimed genus also distinguish members of the genus from others, as required by *Regents of the University of California v. Eli*

Lilly, 43 USPQ2d 1398- (Fed. Cir. 1997). Therefore, the structural requirements of written description are satisfied.

As discussed above, polypeptides comprising SEQ ID NO:9 can be used to identify compounds that inhibit proteolytic activity of brain CPB. Therefore, the specification does describe a function for such polypeptides.

Applicants therefore submit the specification provides sufficient functional and structural descriptions of representative species of the peptide fragments, so that a skilled artisan would recognize Applicants were in possession of the claimed invention.

The Examiner says claim 37 lacks sufficient functional and sufficient written description. In particular, the Examiner says claim 37 is directed to a genus of proteins comprising any polypeptide comprising the motif of SEQ ID NO: 9, wherein, within said motif at least 7 amino acids of SEQ ID NO: 9 are conserved, but alleges the specification does not contain any disclosure of the function of all of said proteins.

As noted above, claim 37 has been amended to recite an isolated peptide consisting of a peptide motif of SEQ ID NO:9, wherein within said motif at least 7 amino acids of SEQ ID NO:9 are conserved. The peptides have a common structural feature, consisting of a motif of SEQ ID NO:9, wherein, within the motif, at least 7 amino acids are conserved. Any species of claim can readily be envisaged. Moreover, the recited structural features serve to distinguish the claimed peptides over any peptides of the prior art. Accordingly, the structural requirements of written description are satisfied.

As noted above, SEQ ID NO:9 is useful for identifying antibodies useful in detecting brain CPB and inhibitors of brain CPB. Peptides having a conserved motif of at least 7 amino acids of SEQ ID NO:9 can be used for the same purpose. Individual peptides may be more, less or equally useful than SEQ ID NO:9. However, any such peptide can be used to narrow down the number of candidates from an initial pool of compounds being screened. Thus, Applicants respectfully submit that the structure and function of peptides within the genus of SEQ ID NO:9 has been described.

The Examiner says claim 38 is directed to a genus of peptides comprising any variant of SEQ ID NO: 9 in which no more than 5 residues have been altered, deleted, inserted

and/or added, but does not contain any disclosure of the function of all such peptides. As discussed above, claim 38 has been amended to recite an isolated peptide variant of SEQ ID NO: 9 consisting of an epitope of human brain carboxypeptidase B, wherein no more than 5 amino acids of SEQ ID NO: 9 are replaced, deleted, inserted and/or added.

Claim 38 satisfies the written description requirement for essentially the same reasons as claim 37. It is possible to envision any variant of SEQ ID NO:9 in which no more than 5 residues have been replaced, deleted, inserted or added. The structural requirement that no more than 5 residues have been deleted, altered or added also serves to distinguish the claimed peptides from any peptides in the prior art. Thus, the structural requirements of written description are satisfied. As discussed above, the variants of SEQ ID NO:9 can be used in the same way as SEQ ID NO:9 itself in generating antibodies to be used in detecting of brain CPB protease. For these reasons, withdrawal of the rejection is respectfully requested.

35 U.S.C. § 102(b)

Claim 37 is rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Fenseelau *et al.* or Napier *et al.* The Examiner alleges Fenseelau *et al.* or Napier *et al.* each disclose a polypeptide comprising the motif of SEQ ID NO:9, wherein, within said motif, 10 or 9 amino acid residues, respectively, of SEQ ID NO:9 are conserved.

Applicants respectfully traverse the rejection as applied to amended claim 37. Claim 37 recites an isolated peptide *consisting of* a peptide motif, wherein, within said motif, at least 7 amino acids of SEQ ID NO:9 are conserved. Neither reference discloses such a peptide. Thus, Applicants respectfully submit a proper *prima facie* case of anticipation has not been established.

Applicants respectfully request the Examiner reconsider and withdraw the rejection of claim 37.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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